

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761195Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)  
Epidemiology: ARIA Sufficiency**

Date: December 15, 2021

Reviewer: Silvia Perez-Vilar, PharmD, PhD  
Division of Epidemiology I

Team Leader: Kira Leishear, PhD, MS  
Division of Epidemiology I

Deputy Division Director: CAPT Sukhminder K. Sandhu, PhD, MPH, MS  
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name: VYVGART™ (efgartigimod alfa – fcab)

Application Type/Number: BLA 761195

Applicant/sponsor: Argenx BV

OSE RCM #: 2021-2292

## Expedited ARIA Sufficiency for Pregnancy Safety Concerns

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### 1. BACKGROUND INFORMATION

#### 1.1. Medical Product

Efgartigimod alfa – fcab (VYVGART™, Argenx BV) is an intravenously administered human IgG1 antibody fragment that binds to the neonatal Fc receptor (FcRn) resulting in the reduction of circulating immunoglobulin G (IgG) including IgG autoantibodies. Efgartigimod does not reduce the levels of other immunoglobulins (IgA, IgD, IgE, or IgM), or those of albumin. Each 20 mL single-dose vial contains 400 mg of efgartigimod alfa – fcab at a concentration of 20 mg/mL. It is a new molecular entity (NME) not currently approved or marketed in any country. The proposed indication is for the treatment of adult patients with generalized myasthenia gravis. VYVGART will be approved for the treatment of adults with generalized myasthenia gravis who are anti-acetylcholine receptor antibody positive. Currently FDA-approved treatments for myasthenia gravis include pyridostigmine bromide and eculizumab. <sup>1</sup> Treatments such as prednisone, azathioprine, mycophenolate mofetil, tacrolimus, rituximab, plasmapheresis, and intravenous immunoglobulin are used off-label. Thymectomy is also a treatment option for some patients. <sup>2</sup>

The proposed dosing regimen for VYVGART is 10 mg/kg as a 1-hour intravenous infusion to be administered in treatment cycles of once weekly infusions for 4 weeks. Efgartigimod alfa – fcab exhibits linear pharmacokinetics and is expected to be degraded by proteolytic enzymes into small peptides and amino acids. The terminal half-life is 80 to 120 hours (3 to 5 days). <sup>3</sup>

The Biologic License Application (BLA) submission included safety data on adults with generalized myasthenia gravis exposed to at least one dose of efgartigimod alfa – fcab during enrollment in an exploratory phase 2, double-blind, placebo-controlled, randomized clinical trial, a pivotal phase 3, double-blind, placebo-controlled, randomized clinical trial, and/or a Phase 3 long-term open label, single-arm multicenter study. Common adverse reactions associated with treatment included respiratory tract infections, urinary tract infections, myalgia, headaches, and hypo/hyperesthesia. <sup>4</sup> The proposed label (as of December 15, 2021) includes warnings and precautions for infections and hypersensitivity reactions. <sup>5</sup>

#### 1.2. Describe the Safety Concern

The Division of Neurology 1 (DN1) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of VYVGART during pregnancy. Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background

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<sup>1</sup> Eculizumab is indicated for treatment of acetylcholine receptor myasthenia gravis, but is not indicated for muscle specific kinase antibody positive or low-density lipoprotein receptor-related protein 4 antibody positive patients.

<sup>2</sup> Efgartigimod alfa – fcab (VYVGART™, Argenx BV). Draft integrated review dated November 23, 2021. Division of Neurology 1. U.S. Food and Drug Administration

<sup>3</sup> Proposed VYVGART labeling dated December 15, 2021

<sup>4</sup> See footnote 2

<sup>5</sup> See footnote 3

risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease Control and Prevention 2008, Food and Drug Administration 2014). Myasthenia gravis is a serious, life-threatening, chronic autoimmune disease in which antibodies bind to acetylcholine receptors, muscle-specific kinase, or lipoprotein-related peptide 4 in the postsynaptic membrane at the neuromuscular junction (Gilhus 2016, Koneczny and Herbst 2019). Different antibodies can result in different subgroups of myasthenia gravis with variable phenotypes and severity. In most patients, the antibodies bind to acetylcholine receptors (Gilhus 2020). Coexisting conditions are common; approximately 15% of patients have a second autoimmune disease, 10% have a thymoma, and although rare, myocarditis occurs with an increased frequency in patients with myasthenia gravis (Gilhus 2016). Myasthenia gravis is a rare disorder, with an estimated prevalence in the general population of 150–250 individuals per million, and with an annual incidence of 8–10 individuals per million. Myasthenia gravis with onset below 50 years, thymic hyperplasia, and acetylcholine receptor antibodies is more common in females than in males. As both prevalence and incidence increase with increasing age, the prevalence and incidence are somewhat lower among females of reproductive age. The muscle weakness, the circulating autoantibodies, the hyperplastic thymus, and any autoimmune comorbidity may influence both mother and child health during pregnancy and also during breastfeeding. Despite this, most pregnancy complications occur with a similar frequency in women with and without myasthenia gravis. However, preterm rupture of amniotic membranes shows an increased frequency, and especially in those with myasthenia gravis deterioration during the pregnancy. Around 10% of the newborn develop neonatal myasthenia during the first few days after birth, which is transient and usually mild. In rare cases, transplacental transfer of acetylcholine receptor antibodies leads to permanent muscle weakness in the child, and arthrogryposis with joint contractures (Gilhus 2020).

There are no data on pregnancy exposure during clinical trials to inform the risk of maternal, fetal, and infant outcomes associated with the use of efgartigimod alfa – fcab.<sup>6</sup> A full battery of reproductive toxicology studies was conducted in Sprague-Dawley rats and New Zealand White rabbits. In all studies, efgartigimod alfa – fcab was administered by intravenous injection at doses of 0, 30, or 100 mg/kg. Efgartigimod alfa – fcab was administered daily to male rats (20/group) beginning 4 weeks prior to mating until the day before sacrifice on study day 43 or 44 and to females (20/group) beginning 2 weeks prior to mating until gestational day 7; there were no effects on the number of females pregnant, females with live fetuses, or the number of resorptions. When pregnant rats (25/group) were administered efgartigimod alfa – fcab daily from gestational day 6 to gestational day 17, no effects on embryofetal development were observed. A slight dose-related increase in pre-implantation loss was noted. Pregnant rabbits (20/group) received efgartigimod alfa – fcab daily from gestational day 6 to gestational day 28. Two low dose females (gestational day 28; 9.1% incidence) and one high dose female (gestational day 20; 4.8% incidence) aborted. This rate was slightly greater than the historical spontaneous abortion rate at this facility ( $4.26\% \pm 4.18$  with a range of 0.0 to 9.5%). There were no significant effects on Cesarean parameters or on embryofetal development. Cerebral hemorrhage was observed in three high dose pups in different litters (15% litter incidence). The total fetal incidence was within the historical control range; however, litter incidence for historical controls was not provided. Another animal study administered efgartigimod alfa – fcab daily to pregnant rats (25/group) from gestational day 6 to lactation day. One pregnant rat who received the high dose died prematurely (gestational day 21). This death was considered due to “incipient abortion.” No test article-related effects were observed on gestation length, gestation index, or preweaning litter parameters (including implantation, liveborn pups,

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<sup>6</sup> See footnote 2



postnatal survival). There were also no drug-related effects on postnatal developmental landmarks or neurobehavioral function. However, the learning and memory evaluation did not include a complex maze as is usually expected. There were no significant effects on mating parameters in offspring or on F2 fetal development. There was a slight reduction in the number of pregnant F1 females, but the effect was not dose-related in magnitude. <sup>7</sup>

The currently proposed labeling, as of December 15, 2021, <sup>8</sup> states in “Section 8.1 (Pregnancy):

“Risk Summary

*There are no available data on the use of VYVGART during pregnancy. There is no evidence of adverse developmental outcomes following the administration of VYVGART at up to 100 mg/kg/day in rats and rabbits (see Data).*

*The background rate of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.*

Clinical Considerations

*Fetal/neonatal adverse reactions*

*Monoclonal antibodies, are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third semester. Therefore, efgartigimod alfa-fcab may be transmitted from the mother to the developing fetus.*

*As VYVGART is expected to reduce maternal IgG antibody levels, reduction in passive protection to the newborn is anticipated. Risk and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to VYVGART in utero [see Warnings and Precautions (5.1)].*

Data

*Animal Data*

*Intravenous administration of efgartigimod alfa-fcab (0, 30, or 100 mg/kg/day) to pregnant rats and rabbits throughout organogenesis resulted in no adverse effects on embryofetal development in either species. The doses tested are 3 and 10 times the recommended human dose (RHD) of 10 mg/kg, on a body weight (mg/kg) basis.*

*Intravenous administration of efgartigimod alfa-fcab (0, 30, or 100 mg/kg/day) to rats throughout gestation and lactation resulted in no adverse effects on pre- or postnatal development. The doses tested are 3 and 10 times the recommended human dose (RHD) of 10 mg/kg, on a body weight (mg/kg) basis.”*

The language in Section 8.2 (Lactation) is as follows:

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<sup>7</sup> Efgartigimod alfa – fcab (VYVGART™, Argenx BV). Non-clinical appendix to draft integrated review dated November 23, 2021. Division of Neurology 1. U.S. Food and Drug Administration

<sup>8</sup> See footnote 3

"Risk Summary"

*There is no information regarding the presence of efgartigimod alfa-fcab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk.*

*The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYVGART and any potential adverse effects on the breastfed infant from VYVGART or from the underlying maternal condition.*

(b) (4)

### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

*- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS*

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

## 2. REVIEW QUESTIONS

### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

### 2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. <sup>†</sup>
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). <sup>†</sup>

<sup>†</sup> **If checked, please complete General ARIA Sufficiency Template.**

### 2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☐ Electronic database study without chart review
- ☒ Other, please specify: Descriptive pregnancy safety study

**2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?**

- ☒ Study Population
- ☐ Exposures
- ☒ Outcomes
- ☒ Covariates
- ☒ Analytical Tools

*For any checked boxes above, please describe briefly:*

Study Population: ARIA lacks the capacity to identify lactating women.

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive, without sample size requirements, and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would collect detailed narratives with information on potential covariates, such as IgG anti-acetylcholine receptor antibodies, baseline motor strength, cardiac and respiratory status, and pulmonary function tests, and lifestyle factors, such as prenatal supplement use and iodine intake.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-born delivery.

**2.5. Please include the proposed PMR language in the approval letter.**

The following language has been proposed by DN1, as of October 28, 2021, for the PMR related to pregnancy outcomes:

*Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to VYVGART (Efgartigimod alfa – fcab) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.*



### 3. REFERENCES

Centers for Disease Control and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep **57**(1): 1-5.

Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved November 24, 2021, from <https://www.fda.gov/media/90160/download>.

Gilhus, N. E. (2016). "Myasthenia Gravis." N Engl J Med **375**(26): 2570-2581.

Gilhus, N. E. (2020). "Myasthenia Gravis Can Have Consequences for Pregnancy and the Developing Child." Front Neurol **11**: 554.

Koneczny, I. and R. Herbst (2019). "Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture." Cells **8**(7).



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/s/  
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SUKHMINDER K SANDHU  
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12/15/2021 04:40:43 PM

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** December 01, 2021

**To:** Rainer Paine, M.D.  
Division of Neurology I (DN I)

Michael Matthews, Regulatory Project Manager, (DN I)

Tracy Peters, Associate Director for Labeling, (DN I)

**From:** Samuel Fasanmi, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, RN, MPH, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Vyvgart (efgartigimod alfa-fcab) injection,  
for intravenous use

**BLA:** 761195

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In response to DN I consult request dated January 19, 2021, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original BLA submission for Vyvgart (efgartigimod alfa-fcab) injection, for intravenous use.

**PI:** OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DN I (Michael Matthews) on November 23, 2021, and are provided below.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 20, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or [samuel.fasanmi@fda.hhs.gov](mailto:samuel.fasanmi@fda.hhs.gov).

15 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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SAMUEL A FASANMI  
12/01/2021 03:51:55 PM

## Clinical Inspection Summary

<b>Date</b>	10/13/2021
<b>From</b>	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief/Acting Division Director Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Michael Matthews, Regulatory Project Manager Rainer Paine, M.D., Medical Officer Laura Jawidzik, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
<b>BLA #</b>	761195
<b>Applicant</b>	Argenx
<b>Drug</b>	Efgartigimod
<b>NME</b>	Yes
<b>Proposed Indication</b>	Treatment of generalized myasthenia gravis in adults
<b>Consultation Request Date</b>	1/25/2021
<b>Summary Goal Date</b>	10/15/2021
<b>Priority/Standard Review</b>	Standard
<b>Action Goal Date</b>	12/17/2021
<b>PDUFA Date</b>	12/17/2021

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Karam, Peric, and Szczechowski were inspected in support of this BLA and covered Protocol ARGX-113-1704. Despite some protocol deviations noted at the sites of Drs. Karam and Peric, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Inspections did not identify any data discrepancies between source and sponsor data line listings for primary efficacy data (Myasthenia Gravis-Activities of Daily Living [MG-ADL] scores) but did identify discrepancies for key secondary efficacy data (Quantitative Myasthenia Gravis [QMG] scores) at the sites of Drs. Karam and Peric. Specifically, QMG individual items for some subjects were incorrectly scored at these sites which impacted the calculation of QMG total scores. The incorrect scores were not identified by the sponsor such that the sponsor data line listings include these errors. We recommend that the review division request that the sponsor review individual item QMG scores and QMG

total scores for all clinical sites and submit corrected datasets for reanalysis by the review division.

Forced vital capacity, assessed via spirometry, was an individual item included in the calculation of the QMG total score. Inspections noted that spirometry results with quality control Grade F (unacceptable spirometer test results) were used in calculating QMG total scores for some subjects. The sponsor had not included any information in the submission regarding the use of Grade F spirometry results in some subjects. This finding was communicated to the review division with the recommendation that the sponsor flag all spirometry results with quality control Grade F (unacceptable spirometer test results) so that adequate review and sensitivity analyses could be conducted to determine any impact on the efficacy analyses for QMG total scores.

## II. BACKGROUND

Efgartigimod injection for intravenous use is being developed under BLA 761195 (IND 132953) for the treatment of adults with generalized Myasthenia Gravis (MG). Efgartigimod is a human IgG1 antibody fragment with affinity to the neonatal Fc receptor resulting in the reduction of circulating IgGs including IgG autoantibodies.

The sponsor has submitted one Phase 3 study (ARGX-113-1704) to support the efficacy and safety of efgartigimod for the treatment of adults with generalized MG.

### Protocol ARGX-113-1704

*Title: "A randomized, double-blind, placebo-controlled multicenter Phase 3 trial to evaluate the efficacy, safety, and tolerability of ARGX-113 [efgartigimod] in patients with myasthenia gravis having generalized muscle weakness"*

*Subjects: 167 randomized*

*Sites: 51 sites in 15 countries; North America (19 sites [US 17]), Eastern Europe (11 sites), Western Europe (9 sites), Asia/Pacific (9 sites), Middle East/Central Asia (3 sites)*

*Study Initiation and Completion Dates: 8/22/2018 to 4/6/2020*

This was a randomized, double-blind, placebo-controlled study in subjects with generalized myasthenia gravis (MG). Included were males or females  $\geq 18$  years of age with a diagnosis of MG (MG Foundation of America clinical classification Class II to IV) with generalized muscle weakness and confirmation of diagnosis supported by at least one of the following:

- History of abnormal neuromuscular transmission demonstrated by single-fiber electromyography or repetitive nerve stimulation, or
- History of positive edrophonium chloride test, or

- Demonstrated improvement in MG signs on oral acetylcholinesterase (AChE) inhibitors as assessed by the treating physician

Additionally, subjects must have a total Myasthenia Gravis Activities of Daily Living (MG-ADL) score of  $\geq 5$  points at screening and baseline with  $>50\%$  of the total score due to non-ocular symptoms, IgG levels  $\geq 6$  g/L at screening, and on a stable dose of their MG medication.

The study was comprised of two phases:

**Screening Phase**– approximately 2 weeks

**Double-Blind Treatment Phase** – 26 weeks

Subjects were randomized (1:1) to one of the following Investigational products (IP) added to concomitant MG medication:

- Efgartigimod (ARGX-113) 10 mg/kg
- Placebo

This 26-week phase included a first Treatment Cycle (TC1) and a variable number of subsequent treatment cycles administered “as needed”. Each treatment cycle consisted of a treatment period of 3 weeks (4 weekly infusions) and a follow-up period of 5 weeks. The time between Treatment Cycles was based on the duration of the treatment effect and varied between and within subjects.

Each subject started a new Treatment Cycle when **all** of the following criteria were met:

- Subject had completed the previous Treatment Cycle
- Subject had a total MG-ADL score  $\geq 5$  points with  $>50\%$  of the total score due to non-ocular symptoms
- The Treatment Cycle can start at the latest on Day 127 and can be completed within the timeframe of the study (26 weeks)
- If the subject lost response – defined as no longer showing a decrease of at least 2 points on the total MG-ADL score compared to the corresponding Treatment Cycle baseline

Randomization was stratified by Japanese vs. non-Japanese, acetylcholine receptor-antibody (AChR-Ab) status (seropositive/seronegative), and non-steroidal immunosuppressive drug use (yes/no). The protocol allowed a maximum of 20% of AChR-Ab seronegative subjects to be enrolled.

The *primary efficacy endpoint* was the percent of MG-ADL responders *after the first Treatment Cycle (TC1)* in the AChR-antibody seropositive population (efgartigimod compared to placebo). MG-ADL responder was defined as a decrease of  $\geq 2$  points from the corresponding treatment cycle baseline on the total MG-ADL score for at least 4 consecutive weeks with the first decrease occurring no later than one week after the last infusion of the corresponding cycle. A *key secondary endpoint* was the percent of Quantitative Myasthenia Gravis (QMG) responders after TC1 in the AChR-antibody seropositive population (efgartigimod compared to placebo). A QMG responder was defined as a decrease of  $\geq 3$  points from the corresponding treatment cycle baseline on the total QMG score for at least 4 consecutive weeks with the first decrease occurring no later than one week after the last infusion of the corresponding cycle.

### Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool and numbers of AChR-Ab seropositive subjects enrolled.

## III. RESULTS

### 1. Chafic Karam, MD

#### Site #USA0012

Oregon Health and Science University  
3181 SW Sam Jackson Park Road  
Portland, OR 97239

Inspection Dates: 4/26/2021 – 5/3/2021

At this site for Protocol ARGX-113-1704, 5 subjects were screened, all of whom were randomized and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, spirometry tracings and reports, concomitant medications, protocol deviations, primary efficacy data (Myasthenia Gravis-Activities of Daily Living scores [MG-ADL]), and key secondary efficacy data (Quantitative Myasthenia Gravis [QMG] scores).

All source documents were in paper format. MG-ADL and QMG scores on source documents were verified against sponsor data line listings. No discrepancies in MG-ADL scores (the primary efficacy endpoint) were identified.

Discrepancies between paper source and sponsor data line listings for QMG individual item scores were identified for four of five randomized subjects (see Table 1). For example, an individual item left hand grip value of 40 seconds was scored as 1 [mild] but should have been scored as 0 [none] which impacted the QMG total score, a key secondary endpoint.

**Table 1. Discrepancies in QMG Individual Item Scores (Site USA0012)**

Subject	Treatment Arm	Treatment Cycle (TC)/ Visit Number	QMG Individual Item		
			Item Description and Result on Source	Correct Score	Incorrect Score in Sponsor Data Listing
(b) (6)	Placebo	TC2V9	Left Hand Grip = 40 KgW	0	1
	Efgartigimod	TC2V3	Head Lifted = 25 seconds	2	1
			Left Leg Outstretched = 22 seconds	2	1
	Efgartigimod	TC1V2	Left Hand Grip = 35.3 KgW	0	1
		TC2V7	Left Hand Grip = 40 KgW	0	1
		TC2V9	Right Leg Outstretched = 26 seconds	2	1
			Left Leg Outstretched = 30 seconds	2	1
	Efgartigimod	TC1V7	Right Arm Outstretched = 76 seconds	2	1
			Left Arm Outstretched = 76 seconds	2	1
		TC1V8	Right Hand Grip = 11 KgW	1	2
			Left Hand Grip = 13 KgW	1	2

The inspection also noted the following:

- For two of five randomized subjects, Forced Vital Capacity (FVC) data from a quality control Grade F (unacceptable spirometer test results) spirometry report were used in the calculation of the QMG.
  - Subject (b) (6), randomized to efgartigimod: 6 of 10 visits in TC1 and 6 of 9 visits in TC2 had a Grade F spirometry report
  - Subject (b) (6) randomized to efgartigimod: 5 of 11 visits in TC1, 3 of 9 visits in TC2 had a Grade F spirometry report

For cases where the spirometry report received a quality control Grade F, the report recommended to repeat the test.



- One of five randomized subjects did not meet criteria for re-treatment. Criteria for re-treatment required a total MG-ADL score of  $\geq 5$  points with  $>50\%$  of the total score due to non-ocular symptoms. Subject (b) (6), randomized to placebo, began cycle two with 50% of the total MG-ADL score due to non-ocular symptoms. This protocol deviation was reported to the sponsor and included in the sponsor data line listings.
- For one of five enrolled subjects, a prior MG medication (IVIG) received by Subject (b) (6) within 12 months prior to screening was not reported to the sponsor. Subject (b) (6) was randomized to efgartigimod.

There was no evidence of underreporting of adverse events and no serious adverse events were reported by this site.

*Reviewer's comment: Discrepancies in QMG total scores were noted for four of five randomized subjects. Three of these study visits occurred in the time period of interest for efficacy analysis, TC1. Due to discrepancies noted at this site and Site SRB0001, we recommend that the review division ask the sponsor to review individual QMG item scores and total QMG scores for all clinical sites and submit corrected datasets.*

*The review division was notified of the use of quality control Grade F spirometry results (unacceptable spirometer test results) in calculating the QMG scores. The sponsor did not flag Grade F spirometry results in the BLA submission or report them as protocol deviations. We recommended that the review division contact the sponsor to obtain these data and perform sensitivity analyses to determine whether these Grade F spirometry results could impact efficacy analyses for QMG total scores.*

## 2. Stojan Peric, MD, PhD

### Site #SRB0001

Clinical Center of Serbia

Clinic for Neurology

Dr Subotica-Starijeg 6

Belgrade, 1100 Serbia

Inspection Dates: 6/14 – 6/18/2021

At this site for Protocol ARGX-113-1704, 26 subjects were screened, 19 were randomized, and 18 subjects completed the study. Subject (b) (6), randomized to efgartigimod, discontinued the study due to the SAE of thrombocytosis. The narrative for this SAE was included in the BLA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents,

monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, spirometry tracings and reports, concomitant medications, protocol deviations, primary efficacy data (MG-ADL scores), and key secondary efficacy data (QMG scores).

All source documents were in paper format. MG-ADL and QMG scores on source documents were verified against sponsor data line listings. No discrepancies were noted for the MG-ADL scores (the primary efficacy endpoint).

Discrepancies between paper source and sponsor data line listings for QMG individual item scores were identified for 3 of 19 randomized subjects (see Table 2). These discrepancies impacted the QMG total score, a key secondary endpoint.

**Table 2. Discrepancies in QMG Individual Item Scores (Site SRB0001)**

Subject/ Gender	Treatment Arm	Treatment Cycle (TC)/ Visit Number	QMG Individual Item		
			Item Description and Result	Correct Score	Incorrect Score in Sponsor Data Listing
(b) (6)	Efgartigimod	TC1V5	Facial Muscles	1	0
	Placebo	TC1V5	FVC, % Predicted = 68	1	2
	Placebo	TC2V8	FVC, % Predicted = 63	2	1

There was no evidence of underreporting of adverse events. One serious adverse event, thrombocytosis, occurred in Subject (b) (6). In compliance with the protocol, this event was reported to the sponsor within 24 hours of the site becoming aware of the event.

*Reviewer comments: Discrepancies in QMG total scores were noted for three of 19 randomized subjects. Two of these study visits occurred in the time period of interest for efficacy analysis, TC1. Due to discrepancies noted at this site and Site USA0012, we recommend that the review division ask the sponsor to review total QMG individual item scores for all clinical sites and submit corrected datasets.*

**3. Lech Szczechowski, MD****Site #POL0007**

Ul. Bolesława Czerwinskiego 8, Nzoż  
Wielospecjalistyczna Poradnia Lekarska  
Synapsis, Katowice  
Poland  
Inspection Dates: 6/21 – 6/24/2021

At this site for Protocol ARGX-113-1704, 21 subjects were screened, and 14 subjects were randomized, all of whom completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records all screened and enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, spirometry tracings and reports, concomitant medications, protocol deviations, primary efficacy data (MG-ADL scores), and key secondary efficacy data (QMG scores).

All source documents were in paper format. MG-ADL and QMG scores on source documents were verified against sponsor data line listings. No discrepancies were noted for MG-ADL scores (the primary efficacy endpoint) or QMG scores (key secondary efficacy endpoint).

Subject [REDACTED] (b) (6), randomized to efgartigimod, was dispensed the incorrect medication kit at TC1V3 due to an error in reading kit numbers by study personnel at the site. This protocol deviation was included in the sponsor line listings as “patient received treatment that was different from the assigned treatment at TC1V3”, without further details. According to sponsor data Listing 16.2.5.1 “Administration of Study Drug”, the actual efgartigimod dose administered at TC1V3 was 680 mg instead of the protocol specified 10 mg/kg dose, i.e., 1040 mg. This subject received the correct dose for all other visits

There was no evidence of underreporting of adverse events, and no serious adverse events were reported by this site.

*Reviewer comment: This isolated dosing error was reported by the sponsor as a deviation but without specific details regarding the total dose administered in the protocol deviation line listing*

*{See appended electronic signature page}*

Cara Alfaro, Pharm.D.  
Clinical Analyst  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Phillip Kronstein, M.D.  
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Kassa Ayalew, M.D., M.P.H  
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**cc:**

Central Document Room/BLA #761195  
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Division of Neurology 1/Medical Officer/Rainer Paine  
Division of Neurology 1/Project Manager/Michael Matthews  
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OSI/Office Deputy Director/Laurie Muldowney  
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew  
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein  
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro  
OSI/GCPAB Program Analyst/Yolanda Patague

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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	September 23, 2021
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	BLA 761195
Product Name and Strength:	Vyvgart (efgartigimod alfa-fcab) Injection, 400 mg/20 mL (20 mg/mL)
Applicant/Sponsor Name:	argenx BV (argenx)
FDA Received Date:	September 7, 2021
OSE RCM #:	2020-2670-2
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader (Acting):	Stephanie DeGraw, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label, carton labeling, and prescribing information received on September 7, 2019 for Vyvgart. The Division of Neurology 1 (DN 1) requested that we review the revised label and labeling for Vyvgart (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

## 2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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<sup>a</sup> Weitzman B. Label and Labeling Review for Vyvgart (BLA 761195). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUL 15. RCM No.: 2020-2670-1.

## APPENDIX A. LABEL AND LABELING RECEIVED ON SEPTEMBER 7, 2021

### A.1 List of Label and Labeling Reviewed

- Prescribing Information (image not shown):  
Available in docuBridge via:  
Clean: <\\CDSESUB1\evsprod\bla761195\0026\m1\us\114-labeling\114a-draft-label\efg-iv-gmg-draft-labeling-text.docx>  
Track changes: <\\CDSESUB1\evsprod\bla761195\0026\m1\us\114-labeling\114a-draft-label\efg-iv-gmg-draft-labeling-text-tc.pdf>
- Container label
- Carton labeling

### A.2 Labeling images

Carton Labeling:

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/  
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STEPHANIE L DEGRAW  
09/23/2021 12:50:23 PM



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MEMORANDUM  
REVIEW OF REVISED LABEL AND LABELING  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 15, 2021
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	BLA 761195
Product Name and Strength:	Vyvgart (efgartigimod alfa-xxxx) <sup>a</sup> Injection, 400 mg/20 mL (20 mg/mL)
Applicant/Sponsor Name:	argenx BV (argenx)
FDA Received Date:	June 18, 2021
OSE RCM #:	2020-2670-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader (Acting):	Celeste Karpow, PharmD, MPH

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<sup>a</sup> The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder “efgartigimod alfa-xxxx” is used throughout this review to refer to the non-proprietary name for this product and not intended to be included in the final labels and labeling.

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 18, 2019 for Vyvgart. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Vyvgart (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>b</sup>

## 2 ASSESSMENT AND RECOMMENDATIONS

Tables 1 below include the identified medication error issues with the submitted container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Comment			
1.	The labels and labeling contain the nonproprietary name suffix placeholder "xxxx."	Once the nonproprietary name with a designated suffix has been found conditionally acceptable, the placeholder "xxxx" should be replaced with the designated suffix.	If the proposed nonproprietary name suffix is found conditionally acceptable, replace the placeholder "xxxx" with the designated suffix to the label and labeling and submit for our review.
Carton Labeling and Container label			
1.	The discard statement is not prominently visible on the carton labeling.	The discard statement "discard unused portion" may be overlooked.	<u>Carton:</u> To increase the readability, we recommend bolding the statement "Discard unused portion" and/or adding the statement to the top flap of the carton.  <u>Container:</u> To increase the readability, we recommend bolding the statement "Discard unused portion."

<sup>b</sup> Weitzman B. Label and Labeling Review for Vyvgart (BLA 761195). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 27. RCM No.: 2020-2670.

Table 1. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The statements, "Do not freeze" and "Do not shake" located on the side panel of the carton label use negative language and are bolded.	Postmarketing reports suggest negative statements may be misinterpreted as an affirmative action if the word "not" is overlooked. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (Available from: <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf</a> ).	We recommend removing the bold font from the negative statements "Do not freeze" and "Do not shake" and revising the statements to read "Avoid freezing and "Avoid shaking."

### 3 CONCLUSION

The revised container label and carton labeling is unacceptable from a medication error perspective. Above, we have provided recommendations in Table 1 for argenx . We ask that the Division convey Table 1 in its entirety to argenx, so the recommendations are implemented prior to approval of this NDA.

APPENDIX A.

- APPLICANT'S RESPONSE TO THE AGENCY'S MAY 27, 2021 COMMENTS RECEIVED ON JUNE 4, 2021

Available in docuBridge via: <\\CDSESUB1\evsprod\bla761195\0014\m1\us\111-info-amend\efg-usa-corr-rtq-18jun2021.pdf>

- IMAGES OF LABEL AND LABELING RECEIVED ON June 18, 2021

Container labels



Carton labeling



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/s/  
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BEVERLY WEITZMAN  
07/15/2021 03:03:23 PM

CELESTE A KARPOW  
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LABEL AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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Date of This Review:	May 27, 2021
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	BLA 761195
Product Name and Strength:	Vyvgart (efgartigimod alfa-xxxx) <sup>a</sup> Injection, 400 mg/20 mL (20 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	argenx BV (argenx)
FDA Received Date:	December 17, 2020 and March 12, 2021
OSE RCM #:	2020-2670
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader (Acting):	Celeste Karpow, PharmD, MPH

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<sup>a</sup> The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder “efgartigimod alfa-xxxx” is used throughout this review to refer to the non-proprietary name for this product and not intended to be included in the final labels and labeling.

## 1 REASON FOR REVIEW

As part of the approval process for Vyvgart (efgartigimod alfa-xxxx) Injection, the Division of Neurology 1 (DN1) requested that we review the proposed Vyvgart prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Information Request	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

\*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information (HPI)			
1.	The Dosage and Administration section of the HPI can be improved.	Improved for clarity.	We recommend you consider the following revisions to the first bullet:  "The recommended dose is 10 mg/kg administered as an intravenous infusion over one hour once weekly for 4 weeks. The maximum total dose per infusion is 1200 mg. (2.1)"

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			In addition, we recommend deleting the third bullet if this information is added to the first bullet as recommended above.
2.	The preparation instruction “dilution prior to administration” is not included in the Dosage and Administration section of the HPI.	We are concerned there is a risk for preparation errors related to dilution if this information is not included in the HPI.	We recommend you consider adding a new bullet to the HPI to remind readers to dilute Vyvgart with 0.9% Sodium Chloride Injection, USP. For example, <ul style="list-style-type: none"> <li>• “Must be diluted with 0.9% Sodium Chloride Injection, USP prior to administration. (2.2)”</li> </ul>
3.	In the Dosage and Administration section of the HPI, the administration technique “via an in-line filter during infusion” is not included.	We are concerned there is a risk for medication errors related to administration.	We recommend adding a new bullet point to remind readers to administer Vyvgart via an in-line and include the specific filter size (e.g., 0.2 micron or 0.22 micron). For example, <ul style="list-style-type: none"> <li>• “Administer as an intravenous infusion over one hour via a XX micron in-line filter. (2.2)”</li> </ul>
4.	In the Dosage Forms and Strengths section of the HPI, the concentration statement (i.e., 20 mg/mL) is not included.	To maintain consistency with the FPI Dosage Forms and Strengths section.	Revise the strength statement to include the concentration (strength per mL) such that the concentration immediately follows the total strength per total volume statement. For example, <p>“Injection: 400 mg in 20 mL (20 mg/mL) single-dose vial”</p>
Full Prescribing Information – Section 2 Dosage and Administration			



Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The paragraph for the recommended dose of Vyvgart in section 2.1 can be revised for clarity.	We are concerned critical dosing information is not presented clearly.	We recommend you consider revising the 2 <sup>nd</sup> paragraph, "The recommended dose of VYVGART (b) (4) is 10 mg/kg as a 1-hour intravenous infusion (b) (4) of once weekly infusions for 4 weeks." to read,  "The recommended dose of VYVGART is 10 mg/kg intravenously over one hour once weekly for 4 weeks. The maximum total dose per infusion is 1200 mg (3 vials)."
2.	There is clinical trial information in section 2.	Section 2 is not the appropriate section for clinical study information.	We recommend you consider deleting the last paragraph (b) (4)  We defer to the division as to what section this information belongs in.
3.	(b) (4) appears in the heading of section 2.2 however the product is a solution (b) (4)	The term (b) (4) may be misleading since Vyvgart Injection is supplied as a solution for dilution.	We recommend you consider revising (b) (4) to read "Preparation and Administration" in the Full Prescribing Information: Contents and "Preparation and Administration Instructions" in the heading for section 2.2.
4.	The placement of the information for the storage of the diluted solution can be improved.	We are concerned the information for the storage of the diluted solution might be overlooked.	We recommend you consider a separate section or subheading titled, "Storage of the Diluted Solution" to appear before the

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			<p>"Administration" subheading for the following bullets:</p> <ul style="list-style-type: none"> <li>• VYVGART does not contain preservatives. Administer immediately after dilution and complete the infusion within 4 hours of dilution.</li> <li>• If immediate use is not possible, the diluted solution may be stored refrigerated at 2°C to 8°C (36°F to 46°F) for up to 8 hours. Do not freeze. Allow the diluted drug to reach room temperature before administration. Complete the infusion within 4 hours of removal from the refrigerator. The diluted drug should not be heated in any manner other than via ambient air.</li> </ul>
5.	<p>The layout of section 2.2 can be improved for clarity.</p> <p>In addition, section 2.2 includes instructions that may not be needed for healthcare providers.</p>	<p>The preparation and administration instructions and layout as presented in section 2.2 are confusing and lack clarity.</p>	<p>See Appendix C for recommendations to section 2.2 for your consideration.</p>
6.	<p>The filter size is not specified in section 2.2.</p>	<p>We are concerned there may be a risk of medication error during administration since there are multiple intravenous in-line filter pore sizes commercially available.</p>	<p>We recommend you consider specifying the filter pore size (e.g., 0.2 micron or 0.22 micron).</p>

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
7.	<p>The following negative statements are in Section 2.2:</p> <p>"Do not administer as a push or bolus injections"</p> <p>"The vial content should not be administered undiluted".</p> <p>"VYVGART contains no preservatives."</p>	<p>We have received post-marketing reports in which negative statements are misinterpreted to mean the opposite of the intended meaning because the word, "not" can be overlooked and the warning may be misinterpreted as an affirmative action<sup>b</sup>.</p>	<p>We recommend you consider revising negative statements to positive language such as:</p> <p>"Infuse the diluted solution continuously over one hour."</p> <p>"Dilute vial contents before administration."</p> <p>"VYVGART is free of preservatives."</p>

Table 3. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The temperature statements do not contain the temperature scale designation (i.e., °C and °F) after each numerical value.	We are concerned this information could be misinterpreted and may pose a risk of drug degradation.	We recommend the degree symbol and temperature scale follow each numeric value denoting temperature ranges, e.g., revise "36-46°F" to read "36°F to 46°F".
2.	As currently presented, the Storage statement lacks prominence.	Lack of prominence of the storage statement may increase the risk of the storage information being overlooked. If the storage information is overlooked this could lead to degradation of the product due to improper storage.	We recommend you increase the prominence of the storage statement taking into account all pertinent factors, including location on the carton and typography. For example, you may consider relocating the storage statement to the principle display panel and back panel and/or bolding.

<sup>b</sup> Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

Table 3. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Also, refer to comment #1 above.
3.	The prominence of the route of administration (i.e., For Intravenous Infusion Only) and the administration technique (i.e., Must dilute before use) can be improved.	Lack of prominence of the route of administration and administration technique may contribute to wrong route of administration errors.	We recommend increasing the prominence of the statements, "For intravenous Infusion Only" and "Must dilute before use" by taking into account all pertinent factors, including bolding, font size, typography, layout, contrast, and other printing features.
4.	The product strength statement includes an additional space before and after the slash mark ("/") sign.	The additional spaces in the strength statement may diminish the readability.	Delete the extra space before and after the slash mark sign in the strength statement. For example: 400 mg/20 mL (20 mg/mL)
5.	The primary strength expression (400 mg/20 mL) can be better distinguished from the concentration expression (20 mg/mL).	A more prominent total strength per volume statement may help users understand the contents of a total vial.	<u>Container:</u> Consider increasing the prominence of the strength per total volume, 400 mg/20 mL, relative to the total strength per mL statement.  <u>Carton:</u> Consider increasing the prominence of the strength per total volume, 400 mg/20 mL and de-bolding the strength per mL statement.  For example: 400 mg/20 mL (20 mg/mL)
6.	The format for expiration date is not defined.	Minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include

Table 3. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			<p>a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.</p> <p>Also refer to “carton labeling” comment #1.</p>
7.	Information regarding post-diluted storage is absent.	We are concerned there is a risk of administering expired product.	If space permits, information on post-diluted storage should also be included on the carton labeling and container label.
Container Label			
1.	The finished dosage form “injection” is absent.	The layout of the finished dosage form is not consistent with the presentation of the proprietary name, proper name, dosage form, and strength for drug products. See Draft Guidance:	<p>Ensure the proper name includes the finished dosage form. Add the finished dosage form “injection” directly below the proper name (i.e., efgartigimod alfa-xxxx).</p> <p><u>For example:</u></p> <p style="text-align: center;">Vyvgart (efgartigimod alfa-xxxx)</p>

Table 3. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		Container and Carton, April 2013 (lines 344-349) <sup>c</sup> .	Injection 400 mg/20 mL (20 mg/mL)
Carton Labeling			
1.	The finished dosage form "injection" is not presented correctly.	The layout of the finished dosage form is not consistent with the presentation of the proprietary name, proper name, dosage form, and strength for drug products. See Draft Guidance: Container and Carton, April 2013 (lines 344-349) <sup>c</sup> .	<u>Carton (PDP, Back Panel and Top Flap):</u> Relocate the dosage form "injection" to appear directly below the proper name.  <u>For example:</u>  <b>Vyvgart</b> (efgartigimod alfa-xxxx) Injection 400 mg/20 mL (20 mg/mL)
2.	The placeholder (XX-XXXX-XX) located immediately above the Global Trade Item Number (GTIN), Serial Number (SN), Lot number and expiration date statements is unclear.	The close proximity of an undefined code near the Global Trade Item Number (GTIN), Serial Number (SN), Lot number and expiration date statements may lead to confusion.	Define the meaning of the undefined code (XX-XXXX-XX) located immediately above the Global Trade Item Number (GTIN), Serial Number (SN), Lot number and expiration date statements.
3.	The lot number statement and the expiration date	The lot number statement should be clearly	Ensure the lot number and expiration are not confused with each other. You may wish

<sup>c</sup> Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Table 3. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	statement ("LOT/EXP") are on the same line.	differentiated from the expiration date statement.	to put the lot number and expiration date statements ("LOT/EXP") appear on separate lines. For example: LOT: EXP:
4.	The color contrast of the white text (i.e., proprietary name and active ingredient) against the (b) (4) background may be insufficient on the top flap of the carton.	Insufficient color contrast may make text difficult to read <sup>d</sup> .	Ensure there is sufficient contrast between the white text and the (b) (4) background color for readability.
5.	The proper name lacks prominence commensurate with the proprietary name.	The prominence of the proper name is not in accordance with 21 CFR 201.10(g)(2).	Increase the prominence of the proper name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
6.	The letter, 'A' in the presentation of the proprietary name does not contain a cross stroke.	The artistic presentation of the letter, 'A' in the presentation of the proprietary name may detract from readability and may distort the interpretation of the proprietary name on the carton.	We recommend you reconsider the font or styling used in the presentation of the proprietary name on the carton.
7.	The dosage statement can be improved.	To ensure consistency with the physician labeling rule	Revise the statement, "See prescribing information for

<sup>d</sup> Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Table 3. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		(PLR) formatted Prescribing Information.	dosage, dilution and administration instructions" to "Recommended Dosage: See prescribing information."
8.	The carton labeling instructs "Must dilute before use". However, the product requires a specific diluent (0.9% sodium chloride injection, USP) which is not specified on the carton labeling.	To help avoid preparation medication errors associated with using a wrong solution for dilution.	We recommend adding the statement "Must be diluted with 0.9% Sodium Chloride Injection, USP prior to use" on the side panel of the carton labeling.
9.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	<p>The DSCSA guidance on product identifiers recommends the format of the human-readable portion be located near the 2D data matrix barcode as follows:</p> <p>NDC: [insert NDC]</p> <p>SERIAL: [insert serial number]</p> <p>LOT: [insert lot number]</p> <p>EXP: [insert expiration date]</p>	<p>We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from:</p> <p><a href="https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf">https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf</a></p> <p>If you determine that the product identifier requirements apply to your product's labeling, add a placeholder for the human- and machine-readable product identifiers to your product's labeling.</p>
10.	The storage instructions "Store in carton" until use and "Protect from light" can be improved.	To improve clarity of the storage instructions.	We recommend you consider rephrasing the storage information "Store in carton until use" and "Protect from light" to "Store in original



Table 3. Identified Issues and Recommendations for argenx BV (argenx) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			carton to protect from light until use."

#### 4 CONCLUSION

Our evaluation of the proposed Vyvgart prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to argenx BV (argenx) so that recommendations are implemented prior to approval of this BLA.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vyvgart received on December 17, 2020 from argenx BV.

Table 4. Relevant Product Information for Vyvgart	
Initial Approval Date	N/A
Active Ingredient	Efgartigimod alfa-xxxx
Indication	For the treatment of adult patients with generalized Myasthenia Gravis (MG).
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	400 mg/20 mL (20 mg/mL)
Dose and Frequency	<ul style="list-style-type: none"> <li>• 10 mg/kg as a 1-hour intravenous infusion to be administered in treatment cycles of once weekly infusions for 4 weeks.</li> <li>• Re-treat patients with treatment cycles of weekly infusions for 4 weeks according to clinical evaluation.</li> <li>• Administer a maximum dose of 1200 mg per infusion in patients weighing 120 kg and over.</li> </ul>
How Supplied	Single dose vials preservative- free concentrated solution
Storage	<p>VYVGART (efgartigimod alfa-xxxx) injection is a sterile, colorless to slightly yellow, clear to slightly opalescent solution concentrate and is supplied in one 20 mL single-dose vial per carton</p> <p>Store VYVGART vials refrigerated at 2°C – 8°C (36°F-46°F) in the original carton to protect from light until time of use. Do not use beyond the expiration date printed on the carton. DO NOT FREEZE. DO NOT SHAKE.</p>
Container Closure	<p>Efgartigimod drug product is filled into (b) (4) glass vials (b) (4). The glass vial is stoppered with a (b) (4) rubber stopper. The container is closed using an aluminum crimp seal equipped with a white (b) (4) flip-off cap.</p>

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 16, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Vyvgart, efgartigimod and BLA 761195. Our search identified zero previous relevant reviews.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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